

A NEW MODEL FOR SOLVING NARROW ESCAPE PROBLEM IN DOMAIN WITH LONG NECK*

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Abstract. The narrow escape problem arises in deriving the asymptotic expansion of the solution of an inhomogeneous mixed Dirichlet-Neumann boundary value problem. In this paper, we mainly deal with narrow escape problem in a smooth domain connected to a long neck-Dendritic spine shape domain, which has a certain significance in biology. Since the special geometry of dendritic spine, we develop a new model for solving this narrow escape problem which is Neumann-Robin Boundary Model. This model transform spine singular domain to smooth spine head domain by inserting Robin boundary condition to the connection part between spine head and neck. We rigorously find the high-order asymptotic expansion of Neumann-Robin Boundary Model and apply it to the solution of narrow escape problem in a dendritic spine shape domain. Our results show that the asymptotic expansion of the Neumann-Robin Boundary Model can be easily applied to the narrow escape problem for any smooth spine head domain with straight spine neck. By numerical simulations, we show that there is great agreement between the results of our Neumann-Robin Boundary Model and the original escape problem. In this paper, we also get some results for non-straight long spine neck case by considering curvature of spine neck.

Key words. narrow escape problem, mean first passage time, Neumann-Robin Boundary Model, asymptotic expansion, mixed boundary value problem, calcium diffusion, dendritic spine

AMS subject classifications. 35B40, 65A05, 92B05

1. Introduction. When a Brownian particle is confined in a bounded domain with a small absorbing windows on an otherwise reflecting boundary, it attempts to escape from this domain through this small absorbing windows. Narrow escape problem is to calculate the mean first passage time Brownian particle takes to get to the absorbing window. From the biological point of view, the Brownian particles could be diffusing ions, globular proteins or cell-surface receptors. It is then of interest to determine, for example, the mean time that an ion requires to find an open ion channel located in the cell membrane or the mean time of a receptor to hit a certain target binding site.

In two dimension, the results of narrow escape problem in smooth bounded domain with one absorbing window was relatively complete [1, 4, 9, 15, 17, 18, 20, 21]. When there are several absorbing windows on the boundary, interaction of multiple absorbing windows are discussed in [10, 12]. In paper [19], several kinds of singular domains have been discussed. In three dimension, the case that bounded domain is a ball with spherical boundary has been discussed in [5, 7].

While, our interest is different from these talked above, but another example of singular domain that a smooth domain connected by a long neck, such as dendritic spine(Fig.1.1). Dendritic spines serve as a storage site for synaptic strength and help transmit electrical signals to the neuron's cell body. As the important site of excitatory synaptic interaction, dendritic spines play an important role in neural plasticity, and their ability to regulate calcium attracts interests of many mathematicians and biologists [2, 3, 6, 8, 14]. Each spine has a bulbous head, and a thin neck that connects the head of the spine to the shaft of the dendrite. We consider simplified model of calcium diffusion in dendritic spines, which is discussed in [13]. That is, first we

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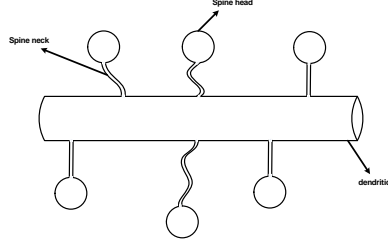
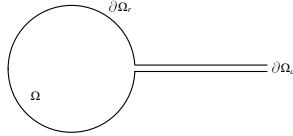


Fig. 1.1: Abstract graph of dendritic spine

Fig. 1.2: The modeling shape of dendritic spine with disk spine head and long spine neck, where Ω is the domain with long neck, $\partial\Omega_r$ is the reflection part, $\partial\Omega_a$ is the absorbing part.

consider the calcium ions to be point charges, furthermore, we assume the motion of ions is free Brownian motion; second, the interaction between two electrostatic ions is neglected; third, we shall simply ignore impenetrable obstacles to the ionic motion posed by the presence of proteins. Thus, the iron motion inside the dendritic spine is geometrically unrestricted. In this paper, we regard the iron as calcium molecule. The calcium diffusion problem is narrow escape problem that is approximated by free Brownian motion in a domain which consists of a spherical head whose length is L and a long cylindrical neck whose radius is a , where the radius of the neck is sufficiently small relative to that of the spine head(Fig.1.2).

In this paper, we only talk about two dimensional case, where spine head is a bounded domain with smooth boundary and spine neck is rectangle, while, Neumann-Robin Boundary Model(1.2) can be easily applied to three dimensions.

The narrow escape problem can be explained explicitly in the following way. Let Ω be a bounded simply connected domain in \mathbb{R}^2 . Suppose that $\partial\Omega$ is decomposed into the reflecting part $\partial\Omega_r$ and the absorbing part $\partial\Omega_a$. We assume that $\varepsilon = |\partial\Omega_a|/2$ is much smaller than the whole boundary(Fig.1.2). The narrow escape problem is to calculate the mean first passage time which is the solution u_ε to (1.1),

$$(1.1) \quad \begin{cases} \Delta u_\varepsilon = -1, & \text{in } \Omega, \\ \frac{\partial u_\varepsilon}{\partial \nu} = 0, & \text{on } \partial\Omega_r, \\ u_\varepsilon = 0, & \text{on } \partial\Omega_a. \end{cases}$$

The asymptotic analysis for narrow escape problem arises in deriving the asymptotic expansion of u_ε as $\varepsilon \rightarrow 0$, from which one can estimate the escape time of the Brownian particle.

In this work, instead of (1.1), we develop another proper model to solve narrow escape problem in dendrite spine shape domain which we call it Neumann-Robin Bound-

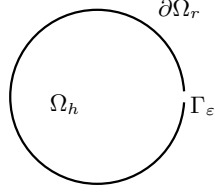


Fig. 1.3: The domain considered in Neumann-Robin model, which omit the long neck by adding Robin boundary condition to small arc Γ_ε , $\partial\Omega_r$ still represents reflecting boundary.

ary Model. The model is described by the following equations in domain Ω_h (Fig.1.3),

$$(1.2) \quad \begin{cases} \Delta u_\varepsilon = -1, & \text{in } \Omega_h, \\ \frac{\partial u_\varepsilon}{\partial \nu} = 0, & \text{on } \partial\Omega_r, \\ \frac{\partial u_\varepsilon}{\partial \nu} + \alpha u_\varepsilon = \beta, & \text{on } \Gamma_\varepsilon := \partial\Omega_h \setminus \overline{\partial\Omega_r}. \end{cases}$$

where Ω_h is the spine head of Ω mentioned in Fig.1.1, the size of Γ_ε is still small with $|\Gamma_\varepsilon| = 2\varepsilon$, but it is not just an absorbing boundary any more. Note that, the domain Ω we considered here is only the head domain, without the neck.

In this paper, we analyze the asymptotic behavior of the solution of Neumann-Robin Boundary Model in the domain Ω_h (see Fig.1.3) in two dimensions. Actually, the asymptotic behavior can be applied to any smooth bounded domain in two dimensions, not only disk case. We rigorously derived the expansion formula for (1.2) up to order $O(\varepsilon)$

$$(1.3) \quad u_\varepsilon(x) = \frac{|\Omega|}{2\alpha\varepsilon} + \frac{|\Omega|}{\pi} \left(\frac{3}{2} + \ln \frac{1}{2\varepsilon} \right) + \frac{\beta}{\alpha} + \Phi_\Omega(x, x^*) + O(\varepsilon).$$

where $\Phi_\Omega(x, x^*)$ can be referred to (3.24).

By assigning specific $\alpha = 1/L$, $\beta = L/2$ to our Neumann-Robin Boundary Model (see the reason for choice of α, β in section 4), the solution formula (1.3) can approximate the mean first passing time of narrow escape problem (1.1) in spine domain (Fig.1.2) up to order $O(\varepsilon)$. The numerical results show a great agreement between them.

This paper is organized as follows. In Section 2, we review the Neumann function for Laplacian and introduce an integral operator for further calculations. In section 3 the asymptotic formula for the solution to Neumann-Robin Boundary Model has been rigorously derived by using layer potential techniques. In section 4 and 5, we discuss how the Neumann-Robin Boundary Model corresponds to the original escape problem theoretically and numerically. The paper ends with a short conclusion.

2. Preliminaries. Let $N(x, z)$ be the Neumann function for $-\Delta$ in Ω corresponding to a Dirac mass at $z \in \Omega$. We assume $\partial\Omega$ is C^2 smooth. $N(x, z)$ is the solution to

$$(2.1) \quad \begin{cases} \Delta_x N(x, z) = -\delta_z, & x \in \Omega, \\ \frac{\partial N}{\partial \nu_x} = -\frac{1}{|\partial\Omega|}, & x \in \partial\Omega, \end{cases}$$

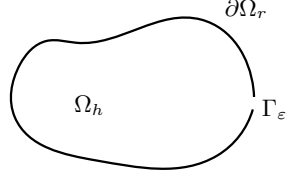


Fig. 3.1: Any smooth domain with small opening Γ_ε . This domain is where Neumann-Robin Boundary Model considered.

For uniqueness, we assume $\int_{\partial\Omega} N(x, z) d\sigma(x) = 0$.

If $z \in \Omega$, $N(x, z)$ can be written in the form

$$(2.2) \quad N(x, z) = -\frac{1}{2\pi} \ln |x - z| + R_\Omega(x, z), \quad x \in \Omega,$$

where $R_\Omega(x, z)$ is the regular part which belongs to $H^{3/2}(\Omega)$, and solves

$$(2.3) \quad \begin{cases} -\Delta_x R_\Omega(x, z) = 0, & x \in \Omega, \\ \frac{\partial R_\Omega}{\partial \nu_x} \Big|_{x \in \partial\Omega} = -\frac{1}{|\partial\Omega|} + \frac{1}{2\pi} \frac{\langle x - z, \nu_x \rangle}{|x - z|^2}, & x \in \partial\Omega. \end{cases}$$

If $z \in \partial\Omega$, Neumann function on the boundary $N_{\partial\Omega}$, can be written as

$$(2.4) \quad N_{\partial\Omega}(x, z) = -\frac{1}{\pi} \ln |x - z| + R_{\partial\Omega}(x, z), \quad x \in \Omega, z \in \partial\Omega,$$

where the singularity of $N_{\partial\Omega}(x, z)$ is $-\frac{1}{\pi} \ln |x - z|$ (See [1]), $R_{\partial\Omega}(x, z)$ solves the problem

$$(2.5) \quad \begin{cases} \Delta_x R_{\partial\Omega}(x, z) = 0, & x \in \Omega, \\ \frac{\partial R_{\partial\Omega}}{\partial \nu_x} \Big|_{x \in \partial\Omega} = -\frac{1}{|\partial\Omega|} + \frac{1}{\pi} \frac{\langle x - z, \nu_x \rangle}{|x - z|^2}, & x \in \partial\Omega, z \in \partial\Omega. \end{cases}$$

Note that the Neumann data above is bounded on $\partial\Omega$ uniformly in $z \in \partial\Omega$ since $\partial\Omega$ is C^2 -smooth, and hence $R_{\partial\Omega}(x, z)$ belongs to $H^{3/2}(\Omega)$ uniformly in $z \in \partial\Omega$. (See [1])

For later use, we introduce the integral operator $L : L^2[-1, 1] \rightarrow L^2[-1, 1]$, defined by

$$L[\phi](x) = \int_{-1}^1 \ln |x - y| \phi(y) dy.$$

We can see operator L is bounded (see Lemma 2.1 in [1]).

3. Neumann-Robin boundary value problem. In this section we rigorously give the asymptotic analysis of our Neumann-Robin Boundary Model in a more general spine head domain Ω_h (Fig. 3.1), where $\Omega_h \in C^2(R^2)$, and derive full expansion solution formula for (1.2) in domain Ω_h up to order $O(\varepsilon)$.

We consider the Laplace equation in Ω_h with the mixed Neumann-Robin boundary condition. The Robin boundary condition is imposed on Γ_ε (Γ_ε is a very small part) and the Neumann boundary condition on the part $\partial\Omega_r := \partial\Omega_h \setminus \overline{\Gamma_\varepsilon}$:

$$(3.1) \quad \begin{cases} \Delta u_\varepsilon = -1, & \text{in } \Omega_h, \\ \frac{\partial u_\varepsilon}{\partial \nu} = 0, & \text{on } \partial\Omega_r, \\ \frac{\partial u_\varepsilon}{\partial \nu} + \alpha u_\varepsilon = \beta, & \text{on } \Gamma_\varepsilon. \end{cases}$$

Here, $\alpha > 0$ and β are given constants. We assume that ε is sufficiently small so that $\alpha\varepsilon \ll 1$ and $\alpha < \alpha_0$ for some constant $\alpha_0 > 0$.

The goal in this section is to derive the asymptotic expansion of u_ε as $\varepsilon \rightarrow 0$, from which one can estimate the exit time of the calcium ion in the spine head.

By integrating the first equation in (3.1) over Ω_h using the divergence theorem we get

$$(3.2) \quad \int_{\Gamma_\varepsilon} \frac{\partial u_\varepsilon}{\partial \nu} d\sigma = -|\Omega_h|.$$

Let us define $g(x)$ by

$$g(x) = \int_{\Omega_h} N(x, z) dz, \quad x \in \Omega_h,$$

which satisfies

$$(3.3) \quad \begin{cases} \Delta g = -1, & \text{in } \Omega_h, \\ \frac{\partial g}{\partial \nu} = -\frac{|\Omega_h|}{|\partial\Omega_h|}, & \text{on } \partial\Omega_h, \\ \int_{\partial\Omega_h} g d\sigma = 0. \end{cases}$$

Therefore, applying the Green's formula to u_ε and the Neumann function N and using (3.1) and (3.3), we get

$$(3.4) \quad u_\varepsilon(x) = g(x) + \int_{\Gamma_\varepsilon} N_{\partial\Omega_h}(x, z) \frac{\partial u_\varepsilon(z)}{\partial \nu_z} d\sigma(z) + C_\varepsilon,$$

where

$$C_\varepsilon = \frac{1}{|\partial\Omega_h|} \int_{\partial\Omega_h} u_\varepsilon(z) d\sigma(z).$$

By (2.4), the equation (3.4) becomes

$$(3.5) \quad u_\varepsilon(x) = g(x) - \frac{1}{\pi} \int_{\Gamma_\varepsilon} \ln|x-z| \frac{\partial u_\varepsilon(z)}{\partial \nu} d\sigma(z) + \int_{\Gamma_\varepsilon} R_{\partial\Omega_h}(x, z) \frac{\partial u_\varepsilon(z)}{\partial \nu} d\sigma(z) + C_\varepsilon.$$

On Γ_ε , by Robin boundary condition, (3.5) can be written as

$$(3.6) \quad \frac{1}{\pi} \int_{\Gamma_\varepsilon} \ln|x-z| \frac{\partial u_\varepsilon(z)}{\partial \nu_z} d\sigma(z) - \int_{\Gamma_\varepsilon} R_{\partial\Omega_h}(x, z) \frac{\partial u_\varepsilon(z)}{\partial \nu_z} d\sigma(z) = \frac{1}{\alpha} \frac{\partial u_\varepsilon(x)}{\partial \nu_x} - \frac{\beta}{\alpha} + g(x) + C_\varepsilon.$$

Let $x(t) : [-\varepsilon, \varepsilon] \rightarrow \mathbb{R}^2$ be the arc-length parametrization of Γ_ε , *i.e.*, $|x'(t)| = 1$ for all $t \in [-\varepsilon, \varepsilon]$ and

$$\Gamma_\varepsilon = \{x(t) \mid t \in [-\varepsilon, \varepsilon]\}.$$

For simplicity, we let

$$(3.7) \quad f(t) = g(x(t)), \quad \phi_\varepsilon(t) = \frac{\partial u_\varepsilon}{\partial \nu}(x(t)), \quad r(t, s) = R_{\partial\Omega_h}(x(t), x(s)).$$

Then it follows from (3.6) that

$$(3.8) \quad \frac{1}{\pi} \int_{-\varepsilon}^{\varepsilon} \ln |x(t) - x(s)| \phi_\varepsilon(s) ds - \int_{-\varepsilon}^{\varepsilon} r(t, s) \phi_\varepsilon(s) ds = \frac{1}{\alpha} \phi_\varepsilon(t) + f(t) + C_\varepsilon - \frac{\beta}{\alpha}.$$

By the change of variable, we obtain

$$(3.9) \quad \frac{1}{\alpha\varepsilon} \tilde{\phi}_\varepsilon(t) - \frac{1}{\pi} \int_{-1}^1 \ln |x(\varepsilon t) - x(\varepsilon s)| \tilde{\phi}_\varepsilon(s) ds + \int_{-1}^1 r(\varepsilon t, \varepsilon s) \tilde{\phi}_\varepsilon(s) ds = -f(\varepsilon t) - C_\varepsilon + \frac{\beta}{\alpha},$$

where $\tilde{\phi}_\varepsilon(t) = \varepsilon \phi_\varepsilon(\varepsilon t)$.

We define two bounded integral operators $L, L_1 : L^2[-1, 1] \rightarrow L^2[-1, 1]$ by

$$L[\phi] = \int_{-1}^1 \ln |t - s| \phi(s) ds,$$

$$L_1[\phi] = \frac{1}{\varepsilon} \int_{-1}^1 \left(\ln \frac{|x(\varepsilon t) - x(\varepsilon s)|}{\varepsilon |t - s|} + \pi r(0, 0) - \pi r(\varepsilon t, \varepsilon s) \right) \phi(s) ds.$$

Since $|x(\varepsilon t) - x(\varepsilon s)| = \varepsilon |t - s| (1 + O(\varepsilon))$, one can see that L_1 is bounded independently of ε .

Using the compatibility condition

$$(3.10) \quad \int_{-1}^1 \tilde{\phi}_\varepsilon(t) dt = -|\Omega_h|,$$

we may write (3.9) as

$$(3.11) \quad \frac{1}{\alpha\varepsilon} \tilde{\phi}_\varepsilon(t) - \frac{1}{\pi} (L + \varepsilon L_1)[\tilde{\phi}_\varepsilon](t) = -\frac{|\Omega_h| \ln \varepsilon}{\pi} + r(0, 0) |\Omega_h| - f(\varepsilon t) - C_\varepsilon + \frac{\beta}{\alpha}.$$

Assume $\alpha < \alpha_0$ and $\alpha\varepsilon \ll 1$. Then we have

$$(3.12) \quad \left(I - \frac{\alpha\varepsilon}{\pi} (L + \varepsilon L_1) \right)^{-1} = I + \frac{\alpha\varepsilon}{\pi} (L + \varepsilon L_1) + O(\alpha^2 \varepsilon^2).$$

Therefore we have

$$(3.13) \quad \tilde{\phi}_\varepsilon(t) = -\alpha\varepsilon \left[I + \frac{\alpha\varepsilon}{\pi} (L + \varepsilon L_1) + O(\alpha^2 \varepsilon^2) \right] \left(C_\varepsilon + \frac{|\Omega_h| \ln \varepsilon}{\pi} - r(0, 0) |\Omega_h| + f(\varepsilon t) - \frac{\beta}{\alpha} \right)$$

$$(3.14) \quad = -\alpha\varepsilon \left[I + \frac{\alpha\varepsilon}{\pi} (L + \varepsilon L_1) + O(\alpha^2 \varepsilon^2) \right] \left(\tilde{C}_\varepsilon + O(\varepsilon) \right),$$

where $\tilde{C}_\varepsilon = C_\varepsilon + \frac{|\Omega_h| \ln \varepsilon}{\pi} - r(0, 0)|\Omega_h| + f(0) - \frac{\beta}{\alpha}$.

By (3.10), we see $\tilde{C}_\varepsilon = O((\alpha\varepsilon)^{-1})$. Then collecting terms we have

$$(3.15) \quad \tilde{\phi}_\varepsilon(t) = -\alpha\varepsilon\tilde{C}_\varepsilon - \frac{(\alpha\varepsilon)^2}{\pi}\tilde{C}_\varepsilon L[1](t) + O(\alpha\varepsilon^2).$$

Plugging it into (3.10) we obtain

$$(3.16) \quad 2\alpha\varepsilon\tilde{C}_\varepsilon + \frac{(\alpha\varepsilon)^2}{\pi}\tilde{C}_\varepsilon \int_{-1}^1 L[1](t)dt = |\Omega_h| + O(\alpha\varepsilon^2).$$

Then we get

$$\begin{aligned} \tilde{C}_\varepsilon &= \left(1 + \frac{\alpha\varepsilon}{2\pi} \int_{-1}^1 L[1](t)dt\right)^{-1} \left(\frac{|\Omega_h|}{2\alpha\varepsilon} + O(\varepsilon)\right) \\ &= \frac{|\Omega_h|}{2\alpha\varepsilon} - \frac{|\Omega_h|}{4\pi} \int_{-1}^1 L[1](t)dt + O(\varepsilon). \end{aligned}$$

The direct calculation shows us

$$\int_{-1}^1 L[1](t)dt = \int_{-1}^1 \int_{-1}^1 \ln|t-y|dtdy = 4\ln 2 - 6.$$

Therefore we arrive at

$$(3.17) \quad \tilde{C}_\varepsilon = \frac{|\Omega_h|}{2\alpha\varepsilon} + \frac{|\Omega_h|}{\pi} \left(\frac{3}{2} - \ln 2\right) + O(\varepsilon),$$

and hence

$$(3.18) \quad C_\varepsilon = \frac{|\Omega_h|}{2\alpha\varepsilon} + \frac{|\Omega_h|}{\pi} \left(\frac{3}{2} + \ln \frac{1}{2\varepsilon}\right) + \frac{\beta}{\alpha} + r(0, 0)|\Omega_h| - f(0) + O(\varepsilon).$$

Substituting (3.17) into (3.15), we have

$$(3.19) \quad \tilde{\phi}_\varepsilon(t) = -\frac{|\Omega_h|}{2} - \frac{|\Omega_h|}{\pi}\alpha\varepsilon \left(\frac{3}{2} - \ln 2 + \frac{1}{2}L[1](t)\right) + O(\alpha\varepsilon^2),$$

and

$$(3.20) \quad \phi_\varepsilon = \frac{1}{\varepsilon}\tilde{\phi}_\varepsilon\left(\frac{t}{\varepsilon}\right) = -\frac{|\Omega|}{2\varepsilon} - \frac{|\Omega|}{\pi}\alpha \left(\frac{3}{2} - \ln 2 + \frac{1}{2}L[1]\left(\frac{t}{\varepsilon}\right)\right) + O(\alpha\varepsilon^{3/2}),$$

where $O(\alpha\varepsilon^2)$ and $O(\alpha\varepsilon^{3/2})$ are measured in $\|\cdot\|_{L^2[-1,1]}$ and $\|\cdot\|_{L^2[-\varepsilon,\varepsilon]}$, respectively.

If x is away from Γ_ε , i.e., $\text{dist}(x, \Gamma_\varepsilon) \geq c$ for some constant $c > 0$, then

$$\begin{aligned} &\int_{\Gamma_\varepsilon} N_{\partial\Omega_h}(x, z) \frac{\partial u_\varepsilon(z)}{\partial \nu_z} d\sigma(z) \\ &= \int_{-\varepsilon}^\varepsilon N_{\partial\Omega_h}(x, z(t)) \left(-\frac{|\Omega_h|}{2\varepsilon} - \frac{|\Omega_h|}{\pi}\alpha \left(\frac{3}{2} - \ln 2 + \frac{1}{2}L[1]\left(\frac{t}{\varepsilon}\right)\right) + O(\alpha\varepsilon^{3/2})\right) dt \\ (3.21) \quad &= -|\Omega_h|N_{\partial\Omega_h}(x, x^*) + O(\varepsilon). \end{aligned}$$

Finally, combining (3.4), (3.18) and (3.21) yields

(3.22)

$$\begin{aligned} u_\varepsilon(x) &= g(x) + \int_{\Gamma_\varepsilon} N_{\partial\Omega_h}(x, z) \frac{\partial u_\varepsilon(z)}{\partial \nu_z} d\sigma(z) + C_\varepsilon \\ &= g(x) - |\Omega| N_{\partial\Omega_h}(x, x^*) + \frac{|\Omega_h|}{2\alpha\varepsilon} + \frac{|\Omega_h|}{\pi} \left(\frac{3}{2} + \ln \frac{1}{2\varepsilon} \right) + \frac{\beta}{\alpha} + r(0, 0)|\Omega_h| - f(0) + O(\varepsilon) \end{aligned}$$

for $x \in \Omega_h$ provided that $\text{dist}(x, \Gamma_\varepsilon) \geq c$ for some constant $c > 0$. Thus we have the following theorem.

THEOREM 3.1. *Suppose that Γ_ε is an arc of center x^* and length 2ε . Then the following asymptotic expansion of u_ε for (3.1) holds*

$$(3.23) \quad u_\varepsilon(x) = \frac{|\Omega_h|}{2\alpha\varepsilon} + \frac{|\Omega_h|}{\pi} \left(\frac{3}{2} + \ln \frac{1}{2\varepsilon} \right) + \frac{\beta}{\alpha} + \Phi_{\Omega_h}(x, x^*) + O(\varepsilon),$$

where

(3.24)

$$\Phi_{\Omega_h}(x, x^*) = \int_{\Omega_h} N(x, z) dz - |\Omega_h| N_{\partial\Omega_h}(x, x^*) - \int_{\Omega_h} N(x^*, z) dz + |\Omega_h| R_{\partial\Omega_h}(x^*, x^*).$$

The remainder $O(\varepsilon)$ is uniform in $x \in \Omega_h$ satisfying $\text{dist}(x, \Gamma_\varepsilon) \geq c$ for some constant $c > 0$. Moreover, if $x(t)$, $-\varepsilon < t < \varepsilon$, is the arclength parameterization of Γ_ε , then,

$$(3.25) \quad \frac{\partial u_\varepsilon}{\partial \nu}(x(t)) = -\frac{|\Omega_h|}{2\varepsilon} - \frac{|\Omega_h|}{\pi} \alpha \left(\frac{3}{2} - \ln 2 + \frac{1}{2} L[1]\left(\frac{t}{\varepsilon}\right) \right) + O(\alpha\varepsilon^{3/2}),$$

where $O(\alpha\varepsilon^{3/2})$ is with respect to $\|\cdot\|_{L^2[-\varepsilon, \varepsilon]}$.

We note that the function $\Phi_{\Omega_h}(x, x^*)$ solves the following problem

$$(3.26) \quad \begin{cases} \Delta_x \Phi_{\Omega_h}(x, x^*) = 0, & x \in \Omega_h, \\ \frac{\partial \Phi_{\Omega_h}(x, x^*)}{\partial \nu_x} = -|\Omega_h| \delta_{x^*}, & x \in \partial\Omega_h. \end{cases}$$

If Ω_h is a unit disk centered at 0, one can easily see from (2.6) and (2.7) that

$$\Phi_{\Omega_h}(x, x^*) = \ln |x - x^*| + \frac{1}{4}(1 - |x|^2).$$

4. Calcium diffusion in dendritic spines. In this section we use our new Neumann-Robin Boundary Model to solve the narrow escape problem in dendritic spine shape domain (Fig. 1.2) which is calcium diffusion problem. That is, we calculate how long a single calcium molecule stays in the spine before it escapes from it.

The usual way to calculate the solution in smooth domain requires boundary layer expansions for small window size and the asymptotic of the Neumann function that worked for nonsingular problems failed for calcium diffusion model since there are two singular points on the connecting part of spine head and spine neck. A quite different approach to the asymptotic problem is required which are much different from those reported in the cited reviews.

In order to approximate the escape time for a particle in spine head, we approach a new method, different from those dealt with in [11, 16], that we use the Neumann-Robin Boundary Model in the spine head domain (Fig. 1.3), but with the specific

$$\alpha = \frac{1}{L}, \beta = \frac{L}{2},$$

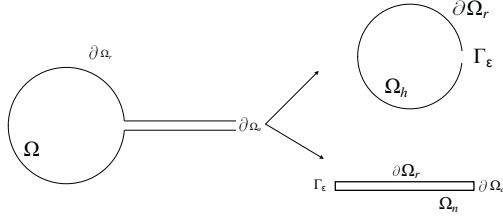


Fig. 4.1: Decompose spine domain into two parts $\Omega = \Omega_h + \Omega_n$. One is spine head domain Ω_h , with reflecting boundary $\partial\Omega_r$ and Robin boundary Γ_ε (where the Neumann-Robin Model can be solved using layer potential techniques in this smooth domain), the other part is long neck Ω_n .

on the boundary Γ_ε which is the opening part of the big head. Here L is the length of the neck. Note that we have changed the domain by dropping the long neck and assigning Robin boundary condition to the connecting arc Γ_ε between the spine head and the long neck. Instead of dealing with the singular part on spine domain, we put a proper Robin boundary to the connecting part between spine head and neck.

The heuristic reason for this specific choice of α and β comes from the following:

In the spine domain, we decompose the domain into two parts, one is spine head which has smooth boundary, the other is the long neck domain (Fig.4.1). Since the spine neck radius is small enough, we assume the escape time on the small part Γ_ε (which connects head and long neck) is constant. Thus, in the spine neck domain Ω_n (Fig.4.1), escape time u_ε satisfies the following equation

$$(4.1) \quad \begin{cases} \Delta u_\varepsilon = -1, & \text{in } \Omega_n, \\ \frac{\partial u_\varepsilon}{\partial \nu} = 0, & \text{on } \partial\Omega_r, \\ u_\varepsilon = 0, & \text{on } \partial\Omega_a, \\ u_\varepsilon = C, & \text{on } \Gamma_\varepsilon, \end{cases}$$

where C is constant whose value means the escape time for the point initiated on Γ_ε . Taking the center point of Γ_ε to be original point $(0,0)$, by separation of variables, we can solve this partial differential equation in Ω_n . The solution of (4.1) is

$$(4.2) \quad u_\varepsilon(x, y) = -\frac{1}{2}(L-x)^2 + \left(\frac{C}{L} + \frac{L}{2}\right)(L-x),$$

where $x \in [0, L]$, $y \in (-\varepsilon, \varepsilon)$. Since Ω_h and Ω_n are connected by Γ_ε , they share the same boundary value. The above solution $u_\varepsilon(x, y)$ satisfies the Robin boundary condition

$$(4.3) \quad \frac{\partial u_\varepsilon}{\partial \nu} + \alpha u_\varepsilon = \beta,$$

with

$$\alpha = \frac{1}{L}, \beta = \frac{L}{2}.$$

Then the approximated Neumann-Robin Boundary Model for narrow escape prob-

lem is:

$$(4.4) \quad \begin{cases} \Delta u_\varepsilon = -1, & \text{in } \Omega_h, \\ \frac{\partial u_\varepsilon}{\partial \nu} = 0, & \text{on } \partial\Omega_r, \\ \frac{\partial u_\varepsilon}{\partial \nu} + \frac{u_\varepsilon}{L} = \frac{L}{2}, & \text{on } \Gamma_\varepsilon, \end{cases}$$

where $u_\varepsilon(x)$ is the escape time of the calcium iron which initiated at x position in the spine head. Ω_h is the domain of the dendritic spine head and $\partial\Omega_r$ means the boundary where calcium molecule is reflected. According to Theorem 3.1 in the last section, the solution to (4.2) is:

$$(4.5) \quad u_\varepsilon(x) = \frac{|\Omega_h|L}{2\varepsilon} + \frac{|\Omega_h|}{\pi} \left(\frac{3}{2} + \ln \frac{1}{2\varepsilon} \right) + \frac{L^2}{2} + \Phi_{\Omega_h}(x, x^*) + O(\varepsilon),$$

where $\Phi_{\Omega_h}(x, x^*)$ is the same as (3.24) for the domain Ω_h .

Suppose that Ω is the spine with straight spine neck domain. The length of the neck is L , and $\partial\Omega_a$ is the exiting arc (See Fig.1.2). Ω_h is the spine head, and Γ_ε is the arc of center x^* which connects spine head and spine neck. The first mean passage time $u_\varepsilon(x)$ of a Brownian particle confined in Ω_h exiting through $\partial\Omega_a$ can be approximated by the following formula

$$(4.6) \quad u_\varepsilon(x) \approx \frac{|\Omega_h|L}{2\varepsilon} + \frac{|\Omega_h|}{\pi} \left(\frac{3}{2} + \ln \frac{1}{2\varepsilon} \right) + \frac{L^2}{2} + \Phi_{\Omega_h}(x, x^*),$$

where $\Phi_{\Omega_h}(x, x^*)$ is the same as (3.24) for the domain Ω_h . The error between formula (4.6) and the exact solution to (1.1) in spine domain is of order $O(\varepsilon)$, which can be seen by the numerical experiment data in the next section.

The method using Neumann-Robin Boundary Model to solve narrow escape problem in domain with long neck is quite different from what has been discussed in [11]. Their idea is to calculate the exit time by separating the exiting process of the particle into two processes. One is the time from the head to the interface Γ_ε between head and neck, the other is the time from the interface to the absorbing arc. The mean first passage time can be obtained by adding the time of these two processes together. Their approximated formulation for planar spine connected to the neck at a right angle is

$$(4.7) \quad u_\varepsilon(x) = \frac{|\Omega_h|}{\pi} \ln \frac{|\partial\Omega_h|}{2\varepsilon} + O(1) + \frac{L^2}{2} + \frac{|\Omega_h|L}{2\varepsilon},$$

where $O(1)$ is the error term. From (4.6) and (4.7), we can see that the results from these two methods have the same first leading order term $\frac{L^2}{2} + \frac{|\Omega_h|L}{2\varepsilon} + \frac{|\Omega_h|}{\pi} \ln \frac{1}{2\varepsilon}$. Thus, using our method we can obtain the exact formula for $O(1)$ in (4.7).

5. Numerical experiment. In order to check whether the asymptotic formula (4.6) can solve the narrow escape problem, we compare the numerical results of (4.6) denoted by u_ε in spine head domain, with the numerical solutions obtained by solving the two dimensional narrow escape problem (1.1) by using Matlab, which is denoted in this section by u . Without loss of generality, we use the approximated spine geometry with unit disk spine head, and a rectangle neck in two dimension.

The first goal in this section is to compare the expansion formula (4.6) and the numerical solution to (1.1). The domain of the escape problem (1.1) is given in Fig.1.2. As one example, we choose the spine head to be unit disk, with the neck

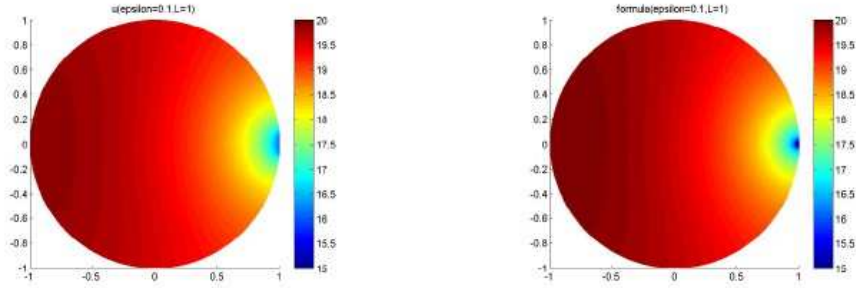


Fig. 5.1: The spine geometry is approximated by a unit disk head and a rectangle neck with width $2\varepsilon = 0.2$ and length $L = 1$. Coordinates represent the position of the iron where it is initiated. The color represents the exit time of particle initiated at this point. Left figure: the numerical result u of (1.1). Right figure: exit time u_ε computed by asymptotic formula (4.6).

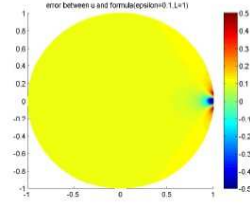


Fig. 5.2: Error between u and u_ε in the above case, where $L = 1$, $\varepsilon = 0.1$.

length $L = 1$, and with the exit arc length $|\partial\Omega_a| = 2\varepsilon$, $\varepsilon = 0.1$. Then, the Neumann-Robin model solve the narrow escape problem in the spine head domain(Fig.1.3). Instead of considering the neck, we put the Robin boundary condition $\frac{\partial u_\varepsilon}{\partial \nu} + \frac{u_\varepsilon}{L} = \frac{L}{2}$ on Γ_ε , where the arc length of Γ_ε is 2ε , $\varepsilon = 0.1$. Note that these two problems have the same spine head domain.

The numerical results are given in Fig. 5.1. The figure on the left side gives the numerical solution to (1.1) in the spine head domain. The value at each point shows the exit time of the particle initiated at this point. We can easily see that if the particle is initiated near the small arc, then it takes less time to escape. On the other hand, the figure on the right side is the numerical result of the expansion formula (4.6). The value at every point represents the exit time of the particle initiated at this point. From these two figures, we can easily see the results in both situations coincide perfectly. The numerical data show that the error between these two situations are of order $O(\varepsilon)$. This will be seen in Table.5.1. Meanwhile, Fig. 5.2 shows the difference

between u and u_ε . The graph shows that away from the exit arc of small distance, u_ε can approximate u with small error of order $O(\varepsilon)$.

The second goal of the experiment is to see whether the Neumann-Robin model can be perfectly applied to solve the escape problem with different radius and different neck length. From Fig. 5.3, we can see the Neumann-Robin model perfectly solves

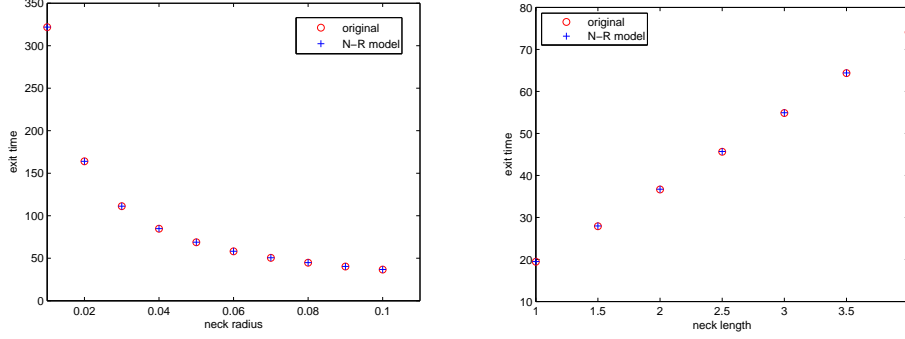


Fig. 5.3: Left figure: Comparison between numerical results of original narrow escape problem (1.1) and expansion formula (4.6) derived from Neumann-Robin model, with different neck radius. We choose head to be unit disk, the neck length to be $L = 2$, vary the neck radius ε from 0.01 to 0.1. Right figure: Comparison between numerical results of original narrow escape problem (1.1) and asymptotic formula (4.6) derived from Neumann-Robin model, with different neck length. Fix head to be unit disk, radius of neck to be $\varepsilon = 0.1$, vary neck length L from 1 to 4.

the escape problem. The numerical solution of these two problems match with each other within error of order $O(\varepsilon)$. The figure on the left side is the case with different radius, 'o' represents the numerical solution of the original narrow escape problem, '+' represents the asymptotic formula (4.6) for Neumann-Robin model. Easy to see they are coincide. The figure on the right side is the case with different neck length. Similarly, the results coincide with each other.

Table 5.1 concretely demonstrates the comparison of these two problems. Releasing the particle at the center of the spine head, Table 5.1 shows the numerical results of the exact solution u , Neumann-Robin model solution u_r and asymptotic formula u_ε , with respect to different neck radius 2ε and neck length L . First, from the comparison of the results in Neumann-Robin model u_r and asymptotic formula u_ε , we can see our derivational calculation for Neumann-Robin problem by using layer potential techniques in section 3 is correct as shown in theorem 3.1. Second, from the comparison between u and u_ε , we can see their difference is of order $O(\varepsilon)$, which means the asymptotic formula can more precisely approximate the exit time.

Next, the domain with non-straight spine neck is considered. Suppose that Ω is the spine domain with a smooth spine neck, Ω_h is the spine head, Γ_ε is an arc of center x^* which connects spine head and spine neck, L is the absolute length of the spine neck, and $\kappa(x)$ is the curvature at the point x . The approximated geometry is the same as the previous situation, but with non-straight neck, see Fig. 5.4.

Through a number of numerical simulations, we find out that the Neumann-Robin model can be easily applied to solve the narrow escape problem in such a situation.

Table 5.1: Comparison result for center point of domain

| ε | L | u_r | u_ε | $u_\varepsilon - u_r$ | u | $u - u_\varepsilon$ | $O(\varepsilon)$ |
|---------------|-----|----------|-----------------|-----------------------|----------|---------------------|------------------|
| 0.1 | 1 | 19.4569 | 19.5136 | -0.0515 | 19.5651 | -0.0567 | 0.1 |
| 0.1 | 1.5 | 27.9232 | 27.9914 | -0.0527 | 28.0441 | -0.0682 | 0.1 |
| 0.1 | 2 | 36.6689 | 36.7189 | -0.0542 | 36.7731 | -0.05 | 0.1 |
| 0.1 | 2.5 | 45.638 | 45.6962 | -0.0558 | 45.752 | -0.0582 | 0.1 |
| 0.1 | 3 | 54.8554 | 54.9235 | -0.0575 | 54.981 | -0.0681 | 0.1 |
| 0.1 | 3.5 | 64.354 | 64.4007 | -0.0593 | 64.46 | -0.0467 | 0.1 |
| 0.1 | 4 | 74.0799 | 74.1279 | -0.0611 | 74.189 | -0.048 | 0.1 |
| 0.09 | 2 | 40.2571 | 40.3195 | -0.0493 | 40.3688 | -0.0624 | 0.09 |
| 0.08 | 2 | 44.7399 | 44.8107 | -0.0437 | 44.8544 | -0.0708 | 0.08 |
| 0.07 | 2 | 50.4918 | 50.5589 | -0.0407 | 50.5996 | -0.0671 | 0.07 |
| 0.06 | 2 | 58.1414 | 58.1882 | -0.0323 | 58.2205 | -0.0468 | 0.06 |
| 0.05 | 2 | 68.7906 | 68.8463 | -0.0273 | 68.8736 | -0.0557 | 0.05 |
| 0.04 | 2 | 84.7263 | 84.7901 | -0.0228 | 84.8129 | -0.0638 | 0.04 |
| 0.03 | 2 | 111.2003 | 111.2612 | -0.0178 | 111.279 | -0.0609 | 0.03 |
| 0.02 | 2 | 163.9653 | 164.0201 | -0.0134 | 164.0335 | -0.0548 | 0.02 |
| 0.01 | 2 | 321.7331 | 321.8301 | -0.0134 | 321.8435 | -0.0504 | 0.01 |

ε : half length of the exit arc. L : length of spine neck. u_r : numerical solution of Neumann-Robin model. u_ε : value of asymptotic formula(4.6). $u_\varepsilon - u_r$: difference between u_ε and u_r . u : numerical solution of narrow escape problem(1.1). $u_\varepsilon - u_r$: difference between u_ε and u_r . $O(\varepsilon)$: error term.

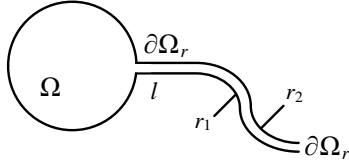


Fig. 5.4: The approximated geometry model of dendritic spine with non-straight long spine neck, where Ω is the domain with long neck, $\partial\Omega_r$ is the reflection part, $\partial\Omega_a$ is the absorbing part. l is the length of straight part of neck. The non-straight part of spine neck is composed of two circle arc, whose radius are r_1 and r_2 respectively.

But because of the curvature on the neck, we need to find a better corresponding neck length, not just the absolute value of the neck length L . We eventually see that if we insert

$$\tilde{L} = L + \varepsilon \int_L \kappa(x) ds$$

into formula (4.6), where L is the absolute length of the neck, $\kappa(x)$ is the curvature of the point x on spine neck, then the Neumann-Robin model in section 3 can approximate the exit time even in the non-straight spine neck case. The first mean passage time $u_\varepsilon(x)$ of a Brownian particle confined in Ω_h exiting through $\partial\Omega_a$ in the

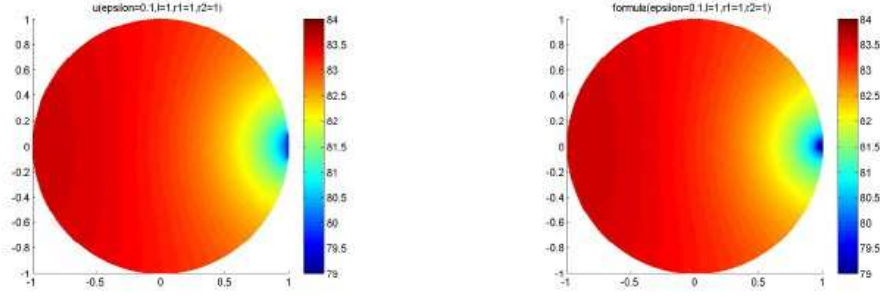


Fig. 5.5: The spine geometry is approximated by a unit disk head, straight neck length $l = 1$ and two quarters of unit disk with exit length $2\varepsilon = 0.2$. Coordinates represent the position of the iron where it is initiated. The color represents the exit time of particle initiated at this point. Left figure: the numerical result u of (1.1). Right figure: exit time computed by asymptotic formula (5.1).

non-straight spine neck domain (Fig.5.4) can be approximated by the formula

$$(5.1) \quad u_\varepsilon(x) \approx \frac{|\Omega_h| \tilde{L}}{2\varepsilon} + \frac{|\Omega_h|}{\pi} \left(\frac{3}{2} + \ln \frac{1}{2\varepsilon} \right) + \frac{\tilde{L}^2}{2} + \Phi_{\Omega_h}(x, x^*),$$

where $\Phi_{\Omega_h}(x, x^*)$ is the same as (3.24) for the domain Ω_h . Our experimental data show that the error between this formula (5.1) and the exact solution for (1.1) in the non-straight spine neck domain is of order $O(\varepsilon)$.

There is one example. Consider the domain (Fig.5.4) which is composed of unit disk head, the straight neck part $l = 1$, non-straight part $r_1 = 1$, $r_2 = 1$, and exit arc length 2ε , $\varepsilon = 0.1$. The numerical results of the solution u for (1.1) and the result u_ε of the expansion formula (5.1) with $\tilde{L} = L + \varepsilon \int_L \kappa(x) ds$ are given in Fig.5.5.

The figure on the left side gives the numerical solution u of (1.1) in the spine head domain. The value at each point means the exit time of the particle initiated at that point. The figure on the right side is the solution u_ε for asymptotic formula (5.1) with the neck length \tilde{L} . From these two figures, we can easily see the results in both situations agree within a small error. The numerical data show that the error between these two situations are of order $O(\varepsilon)$. Meanwhile, Fig. 5.6 shows the difference between u and u_ε . The graph shows that away from the exit arc of small distance, u_ε can approximate u within small error of order $O(\varepsilon)$. The data of Table 5.2 also confirm this assertion.

6. Conclusion. In this paper, using Neumann-Robin Boundary Model we transform spine singular domain to smooth spine head domain. We provided mathematically rigorous derivation of the leading order term in the asymptotic expansion of the solution of Neumann-Robin Boundary Model which we invented to solve narrow escape problem in domain with long neck. The result shows that using this model we find first escape time up to order $O(\varepsilon)$ which is not found in other papers. The

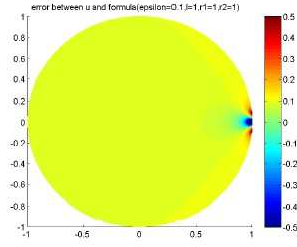


Fig. 5.6: Error between u and u_ε in the above case, where $\varepsilon = 0.1$, $l = 1$, $r_1 = 1$, $r_2 = 1$.

Table 5.2: Comparison result for center point of domain

| ε | l | r_1 | r_2 | u | u_ε | $u_\varepsilon - u$ | $O(\varepsilon)$ |
|---------------|-----|-------|-------|----------|-----------------|---------------------|------------------|
| 0.1 | 1 | 0.7 | 0.9 | 70.4851 | 70.7957 | 0.3106 | 0.1 |
| 0.1 | 1.5 | 0.7 | 0.9 | 80.36 | 80.6873 | 0.3273 | 0.1 |
| 0.1 | 2 | 0.7 | 0.9 | 90.5009 | 90.8358 | 0.3349 | 0.1 |
| 0.1 | 1 | 1 | 1 | 82.9631 | 83.253 | 0.2899 | 0.1 |
| 0.05 | 1 | 1 | 1 | 148.1522 | 148.3267 | 0.1745 | 0.05 |
| 0.05 | 2 | 1 | 1 | 184.3655 | 184.5477 | 0.1822 | 0.05 |
| 0.05 | 3 | 1 | 1 | 221.5875 | 221.7754 | 0.1879 | 0.05 |

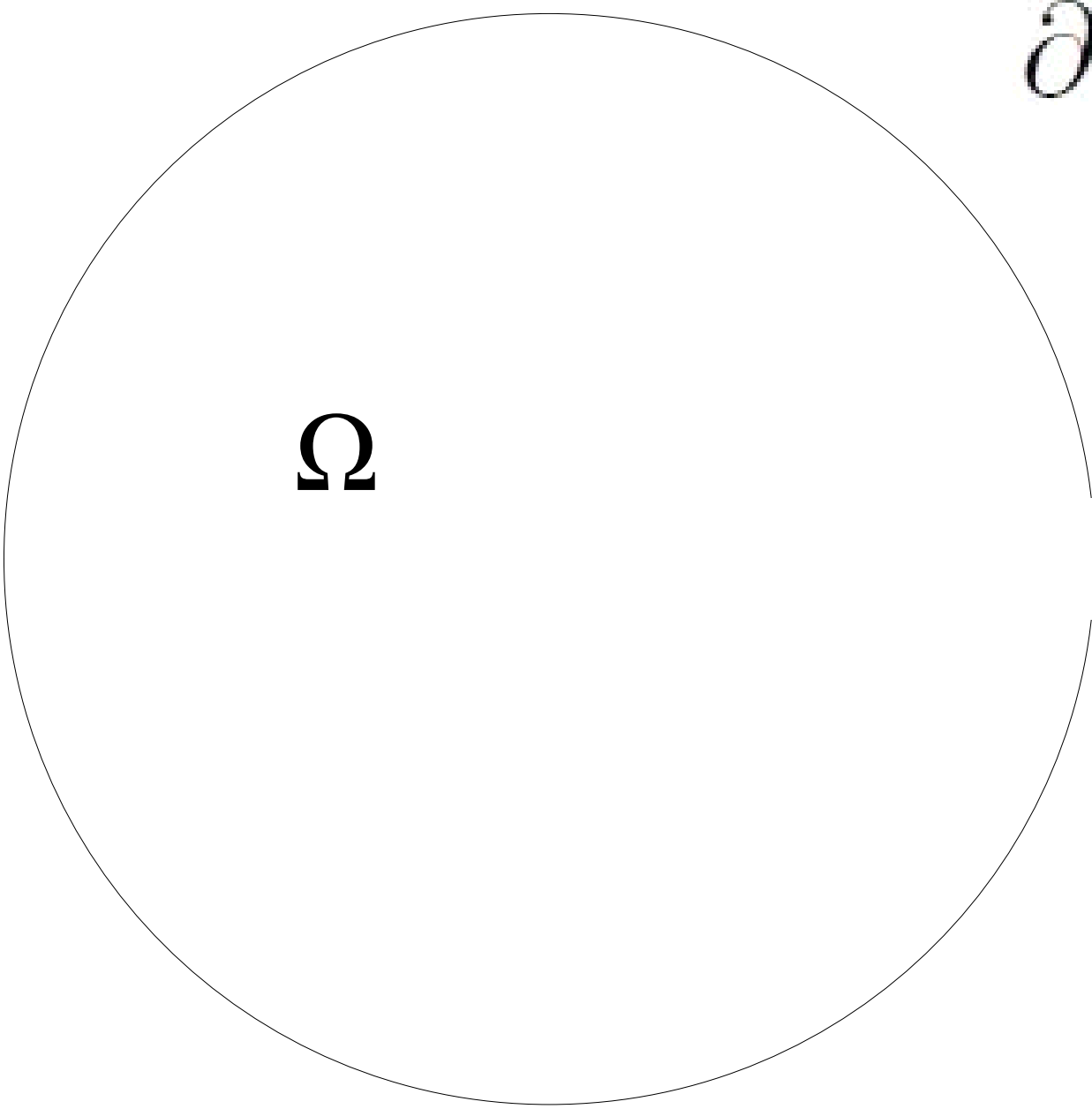
ε : half length of the exit arc. l : length of straight part of spine neck. r_1 and r_2 : the radius of two circles. u_ε : value of asymptotic formula(5.1). u : numerical solution of narrow escape problem(1.1). $u_\varepsilon - u$: difference between u_ε and u . $O(\varepsilon)$: error term.

solution to the Neumann-Robin Boundary Model in the spine head domain can be easily applied to the calcium diffusion model of the narrow escape problem, one with straight spine neck and the other with non-straight spine neck. As for the non-straight spine neck, integrating the neck curvature we can get an effective length which can be put into our explicit expansion formula of Neumann-Robin Boundary Model and get the approximated exit time. This Neumann-Robin Model can be extended to three dimension. Because of the existence of long neck the operators we defined in section 3 can be shown bounded and expansion formula can be similarly derived with two dimensional case. What's more, for narrow escape problem in three dimensional smooth domain with exit on the boundary, since the difficulty in 3D case, up to now, only spherical cases are appeared in other papers. But for any other smooth domain in 3D, even it has no long neck, we can still use this Neumann-Robin Boundary Model by punching long neck to the small exit on the boundary which will be the subject of a forthcoming paper.

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REFERENCES

- [1] H. AMMARI, H. KANG, H. LEE, *Layer potential techniques for the narrow escape problem*, J. Math. Pures Appl.(9), 97(2012), pp. 66–84.
- [2] A. M. BEREZHKOVSII, A. V. BARZYKIN, V. Y. ZITSERMAN, *Escape from cavity through narrow tunnel*, J. Chem. Phys., 130(2009), pp. 245104.
- [3] A. BIESS, E. KORKOTIAN, D. HOLCMAN, *Diffusion in a dendritic spine: The role of geometry*, Phys. Rev. E(3), 76(2007), pp. 021922.
- [4] X. CHEN, CAREY CAGINALP, *Analytical and numerical results for first escape time in 2D*, C. R. Acad. Sci. Paris, 349(2011), pp. 191194.
- [5] X. CHEN, A. FRIEDMAN, *Asymptotic analysis for the narrow escape problem*, SIAM J. Math. Anal. 43(2011), pp. 2542–2563.
- [6] Y. CHEN, B. L. SABATINI, *Signaling in dendritic spines and spine microdomains*, Curr Opin Neurobiol., 22(2012), pp. 389–396.
- [7] A. CHEVIAKOV, M. WARD, R. STRAUBE, *An asymptotic analysis of the mean first passage time for narrow escape problems: Part II: The sphere*, Multiscale Model. Simul., 8(2010), pp. 836–870.
- [8] D. HOLCMAN, E. KORKOTIAN, M. SEGAL, *Calcium dynamics in dendritic spines, modeling and experiments*, Cell Calcium, 37(2005), pp. 467–475.
- [9] D. HOLCMAN, Z. SCHUSS, *Escape through a small opening: receptor trafficking in a synaptic membrane*, J. Stat. Phys., 117(2004), pp. 975–1014.
- [10] D. HOLCMAN, Z. SCHUSS, *Diffusion escape through a cluster of small absorbing windows*, J. Phys. A: Math. Theor., 41(2008), pp. 155001.
- [11] D. HOLCMAN, Z. SCHUSS, *Diffusion laws in dendritic spines*, J. Math. Neurosci., (2011), pp. 1–10.
- [12] D. HOLCMAN, Z. SCHUSS, *Diffusion through a cluster of small windows and flux regulation in microdomains*, Phys. Lett. A, 372(2008), pp. 3768–3772.
- [13] D. HOLCMAN, Z. SCHUSS, *Modeling calcium dynamics in dendritic spines*, SIAM J. Appl. Math. 65(2004), pp. 1006–1026.
- [14] D. HOLCMAN, Z. SCHUSS, E. KORKOTIAN, *Calcium dynamics in dendritic spines and spine motility*, Biophys J., 87(2004), pp. 81–91.
- [15] S. PILLAY, M. J. WARD, A. PEIRCE, T. KOLOKOLNIKOV, *An asymptotic analysis of the mean first passage time for the narrow escape problems: Part I: two-dimensional domain*, Multiscale Model. Simul., 8(2009), pp. 803–835.
- [16] Z. SCHUSS, *The narrow escape problem-a short review of recent results*, J. Sci. Comput., 53(2012), pp. 194–210.
- [17] Z. SCHUSS, A. SINGER, D. HOLCMAN, *The narrow escape problem for diffusion in cellular microdomains*, Proc. Nat. Acad. Sci., 104 (2007), pp. 16098–16103.
- [18] A. SINGER, Z. SCHUSS, D. HOLCMAN, R. S. EISENBERG, *Narrow escape. Part I.*, J. Stat. Phys., 122(2006), pp. 437–463.
- [19] A. SINGER, Z. SCHUSS, D. HOLCMAN, *Narrow escape. III. Non-smooth domains and Riemann surfaces*, J. Stat. Phys. 122(2006), pp. 491–509.
- [20] A. SINGER, Z. SCHUSS, D. HOLCMAN, *Narrow escape and leakage of Brownian particles*, Phys. Rev. E, 78(2008), pp. 051111.
- [21] A. TAFLIA, D. HOLCMAN, *Dwell time of a Brownian molecule in a microdomain with traps and a small hole on the boundary*, J. Chem. Phys, 126(2007), pp. 234107.



Ω

$\partial\Omega_r$

Γ_ε

